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Tobacco smoking, *NAT2* acetylation genotype and breast cancer risk

Jolanta Lissowska[1,2]*, Louise A. Brinton[2], Witold Zatonski[1], Aaron Blair[2], Alicja Bardin-Mikolajczak[1], Beata Peplonska[3], Mark E. Sherman[2], Neonila Szeszenia-Dąbrowska[3], Stephen Chanock[4] and Montserrat García-Closas[2]

[1]*Department of Cancer Epidemiology and Prevention, Cancer Center and M. Sklodowska-Curie Institute of Oncology, Warsaw, Poland*
[2]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD*
[3]*Nofer Institute of Occupational Medicine, Lódź, Poland*
[4]*Core Genotyping Facility, National Cancer Institute, National Institutes of Health, Gaithersburg, MD*

The role of active and passive cigarette smoking in breast cancer etiology remains controversial. Using data from a large population-based case-control study in Poland (2386 cases, 2502 controls) conducted during 2000–2003, we examined the associations between active and passive smoking overall and for different age categories. We also evaluated differences in risk by estrogen receptor (ER) and progesterone receptor (PR) status in tumors, and the potential modification of the smoking association by *N*-acetyl transferase 2 (*NAT2*) genotype. Women ever exposed to passive smoking at home or at work had a risk of breast cancer similar to those never exposed to active or passive smoking (OR (95%CI) = 1.11 (0.85–1.46), and no trends were observed with increasing hours/day-years of passive smoking exposure. Active smoking was associated with a significant increase in risk only among women younger than 45 years of age (OR (95%CI) = 1.95 (1.38–2.76); 1.15 (0.93–1.40); 0.91 (0.77–1.09) for <45, 45–55 and >55 years of age, respectively; *p*-heterogeneity <0.001 for <45 *vs.* >55 years) and prevailed for both ER+ and ER− tumors. The smoking association among women <45 years was stronger for current than former smokers, and a significant trend was observed with duration of smoking ($p = 0.04$). *NAT2* slow *vs.* rapid/intermediate acetylation genotype was not related to breast cancer risk (0.99 (0.87–1.13)), and did not significantly modify the smoking relationships. In conclusion, our data indicate that passive smoking is not associated with breast cancer risk; however, active smoking might be associated with an increased risk for early onset breast cancers.

Key words: breast cancer; smoking; hormone receptor status; *NAT2*

The relationship between cigarette smoking and breast cancer risk is still uncertain. Recently published reviews[1,2] and meta-analyses[3–5] have found that active cigarette smoking is not related to a substantial overall increased risk of developing breast cancer. However, several studies, including three large cohort studies,[6–8] have suggested associations of breast cancer risk with heavy smoking, early ages at initiation, exposures prior to first full-term pregnancy or after long latency periods.[7,9]

Paradoxically, passive smoking has been suggested to increase risk by a similar magnitude of risk as has been found for active smoking.[1,4] There is some controversy as to whether the lack of association for active smoking, observed in most earlier studies, might be due to the fact that passive smokers were included in the referent groups. Indeed, some more recent studies show modest associations for active smokers compared to women never exposed to active or passive smoking.[2,6,9–11] Given that passive smoking is difficult to measure, and that most studies have had incomplete information, a relationship between passive smoking and breast cancer is still unclear.

Biological evidence indicates that tobacco smoke is a plausible mammary carcinogen. Tobacco smoke contains multiple fat-soluble compounds that are known to induce mammary tumors in rodents,[12] can be found in human breast fluid[13] and can remain concentrated in the human mammary duct for a long time.[14,15] Smoking might affect breast cancer risk through direct carcinogenic effects, a notion supported by findings of polycyclic aromatic hydrocarbon and 4-aminobiphenyl DNA adducts in breast tissue of smokers.[16,17] A hormonally related mechanism has also been suggested, given findings of altered estrogen metabolites among smokers.[18]

Accumulating data suggest that major known risk factors for breast cancer may vary by age at diagnosis[19,20] and hormone receptor status.[21,22] Competing effects of tobacco smoke on breast cancer risk, *i.e.*, carcinogenic in premenopausal women and antiestrogenic in postmenopausal women, support that age at diagnosis and hormonal status might modify smoking relationships with breast cancer risk. Because constituents of tobacco smoke can bind to estrogen receptors (ERs),[23] some studies have suggested that cigarette smoking may be more strongly associated with ER positive tumors,[24,25] although not all investigations have confirmed this.[21,26]

A number of studies have suggested that the association between active smoking and breast cancer risk may be limited to women with certain genetic predispositions.[2,27,28] Most notably, some studies suggest that women with the slow acetylation phenotype for *N*-acetyltransferase 2 (*NAT2*), an enzyme that metabolizes aromatic amines in tobacco smoke, may be more adversely affected by tobacco smoking,[29–31] but data have been inconsistent.[32,33]

We investigated the associations between passive and active smoking and breast cancer risk in a large population-based case-control study in Poland. Detailed information on lifetime exposures to both passive and active smoking and the large size of our study enabled specific assessment of risk according to age, tumor receptor status, and *NAT2* genotype. Evaluation of the relationship between smoking and breast cancer in this population is particularly relevant because breast cancer is the most common cancer (42 new cases per 100,000 women in 2002) and cause of cancer death (13% of cancer deaths in 2002)[34] in Polish women, and smoking prevalence is increasing, especially among younger women: the percentage of smokers among women younger than 49 years of age has increased from less than 20% in 1974 to almost 40% in 2004.[35]

Material and methods

The data were derived from a large population-based case control study conducted in the two largest cities of Poland (Warsaw and Łódź). The design of this study has been described in detail elsewhere.[36] Eligible cases were female residents of Warsaw or Łódź aged 20–74 years who were diagnosed between January 1, 2000 and January 31, 2003 with either histologically or cytologically confirmed incident *in situ* or invasive breast cancer. Cases were recruited through a rapid identification system organized at five participating hospitals, covering about 90% of all breast cancer cases diagnosed in the two cities. In addition, the Cancer Registry files were reviewed regularly to identify cases that were

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***Correspondence to:** Department of Cancer Epidemiology and Prevention, Cancer Center and M. Sklodowska-Curie Institute of Oncology, Warsaw, Poland. E-mail: lissowsj@coi.waw.pl
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missed by the rapid identification system. Eligible control subjects were residents of Warsaw and Łódź who did not have a history of breast cancer at enrollment. The Polish Electronic System, a data base with demographic information from all residents of Poland, was used to randomly select controls matched to cases on city and age in 5-year categories. Personal interviews collected information on known or suspected breast cancer risk factors, including both active and passive lifetime smoking histories, from 79% of eligible cases and 69% of controls. This resulted in a total of 2386 cases and 2502 controls included in the analyses.

Clinical data from breast cancer patients, including diagnostic and treatment procedures and ER and progesterone receptor (PR) status of the tumors, were abstracted from the medical records. ER/PR status was determined by immunohistochemistry in most cases (90%) and by biochemical methods for the remainder (10%). A single pathologist in the U.S. (M.E.S) performed a microscopic review of tumor slides to provide standardized diagnoses.

Smoking information

Ever-active smokers were defined as women who smoked a total of 100 or more cigarettes in their lifetimes, and who smoked on a regular basis (defined as smoking at least 1 cigarette per day for 6 months or longer). Active smokers on the reference date (date of diagnosis for cases and date of interview for controls) or those who stopped smoking during the past year were considered current smokers. Those who stopped smoking more than one year prior to the reference date were considered former smokers. Among ever-active smokers, information was collected on years started and stopped, and average number of cigarettes smoked per day (for each self-defined period).

Information on passive smoking was collected for exposures at home and at work. For exposures at home, information was elicited on how many smoking relatives had lived in the household at different times, when smoking began, number of cigarettes smoked per day, years of exposure and the number of hours and days each of the relatives had smoked in the presence of the subject. Passive exposure at work was assessed separately for each job held for 6 months or longer. Information was sought on the number of hours per day or week spent with smokers in the work environment, number of smokers at work (3 categories: 1–2, 3–5, 6 or more) and subjective evaluation of the intensity of exposure (3 categories: light, moderate, intense). Passive smokers were defined as women who reported having been exposed to passive smoke at home and/or at work at least 1 hr per day for at least 1 year.

NAT2 *genotyping*

Most women (84% of cases and 94% of controls) who agreed to the interview also provided a blood sample. Genomic DNA for genotype analyses was isolated from buffy coat or whole blood samples from these women (1,995 cases and 2,296 controls) using the Autopure LS® DNA Purification System (Gentra Systems, Minneapolis, MN). Genotype assays were performed at the Core Genotyping Facility of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, using the Applied Biosystems TaqMan (Foster City, CA).

Genotype assays were performed for *NAT2 K268R* rs1208, *G286E* rs1799931, *R64Q* rs1801279, *Y94Y* rs1041983, *I114T* rs1801280, *L161L* rs1799929 and *R197Q* rs1799930. Descriptions and methods for each specific assay can be found at http://snp500cancer.nci.nih.gov. All genotypes under study were in Hardy-Weinberg equilibrium in the control population, and duplicate quality control samples showed 98% or greater agreement for all assays. Information from the *NAT2* SNPs analyzed was used to assign the most likely *NAT2* alleles previously identified in human populations[37] (updated at www.louisville.edu/medschool/pharmacology/NAT.html). Individuals homozygous for rapid *NAT2* acetylator alleles (*NAT2*4*, *NAT2*11A*, *NAT2*12A*, *NAT2*12B*, *NAT2*12C*, *NAT2*13*) were classified as rapid acetylator phenotype; individuals homozygous for slow acetylator alleles were classified as slow acetylator phenotypes and heterozygous individuals (one rapid and one slow *NAT2* allele) were classified as intermediate acetylator phenotypes.

Statistical analyses

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer risk in relation to smoking characteristics, adjusting for matching factors (age in 5-year age-groups and study site) and potential confounders, including years of education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, body mass index (BMI = weight (kg)/(height (m))^2), family history of breast cancer, prior benign breast biopsy, oral contraceptive use and use of hormone replacement therapy. Additional adjustment for alcohol use did not appreciably change OR estimates; therefore, it was not included in the final models.

Subjects exposed to passive smoking were categorized as those with exposure only at home, exposure only at work and exposure both at home and work. We used ''hours per day-years'' as a measure of intensity and duration of exposure to passive smoking either at home or work, as proposed by Morabia *et al.*[38] This variable was obtained by summing ''hours/day $\times$ duration'' for all periods of passive exposure at home or work.

We evaluated the relationship between breast cancer risk and increasing levels of smoking dose and intensity, compared to never smoking women. Smoking intensity and duration were adjusted for each other by combining never smokers with the lowest smoking duration category to obtain estimates of dose adjusted for duration and vice versa. Tests for trend were performed, among exposed women only, for age at initiation of smoking, average number of cigarettes smoked per day, duration and pack-years smoked. Categories were scored by the median value in each category.

We evaluated whether active or passive smoking influences breast cancer risk differently in women diagnosed at ages <45, 45–55 and >55 years. These categories were chosen to approximate pre-, peri- and postmenopausal status. Heterogeneity of smoking status (ever, former, current *versus* never) by age categories was tested by introducing interaction terms in logistic regression analyses. Heterogeneity of smoking dose, intensity and age started smoking by age categories was tested assuming a log-linear relationship between increasing levels of exposure and breast cancer risk, within each age category, *i.e.* we introduced interaction terms for exposure as a ''continuous'' variable (categories weighted by their median value) and age categories. Heterogeneity for smoking initiation in relation to first pregnancy was tested using a 2-degrees for freedom likelihood ratio test (LRT) comparing a model with interaction terms for age and indicator terms for smoking initiation before or after pregnancy to a model without these interactions terms.

We also evaluated interactions between smoking characteristics and *NAT2* acetylation genotype. A LRT comparing regression models with and without interaction terms was used as a test for interaction. Heterogeneity of risk factor ORs for tumors with different ER/PR receptor status was tested using logistic regression analyses for cases only with receptor status as the outcome variable. Estimates of risk for different tumor subtypes were derived from polytomous logistic regression models.

Results

About 50% of controls reported both active and passive smoking exposure, an additional 40% reported passive exposure only and a small percentage reported no active or passive (6%) smoking, or only active (4%) smoking (Table I). Similar distributions were seen among cases. Among lifetime never-active smokers, approximately 75% of cases and 78% of controls reported ever being exposed to passive smoking at home, whereas 49% of cases and 44% of controls reported some passive smoking at work.

Breast cancer risk was not significantly elevated for women ever exposed to passive or active smoking compared to women

TABLE I – PASSIVE AND ACTIVE SMOKING AND BREAST CANCER RISK IN THE POLISH BREAST CANCER STUDY (2386 CASES AND 2502 CONTROLS)

	Cases[1]	Controls[1]	OR[2]	95% CI
Active or passive smoking status				
All women				
Never active/passive smoking	124	150	1.00	(reference)
Only passive smoking (work or home)	910	1012	1.11	0.85–1.46
Only active smoking	94	91	1.23	0.83–1.83
Active and passive smoking	1246	1243	1.21	0.93–1.59
Age <45 years				
Never active/passive smoking	9	17	1.00	
Only passive smoking (work or home)	86	116	1.28	0.52–3.11
Only active, or active and passive smoking	208	168	2.40	1.00–5.72
Age 45–55				
Never active/passive smoking	34	44	1.00	
Only passive smoking (work or home)	265	280	1.27	0.76–2.11
Only active, or active and passive smoking	644	655	1.40	0.86–2.30
Age >55				
Never active/passive smoking	81	89	1.00	
Only passive smoking (work or home)	559	614	1.04	0.74–1.46
Only active, or active and passive smoking	488	491	0.98	0.69–1.38
Passive smoking characteristics among never active smokers (1034 cases, 1162 controls)				
Never active/passive smoking	124	150	1.00	(reference)
Ever passive exposure at home or work	910	1012	1.10	0.84–1.45
At home only	389	489	1.08	0.80–1.46
At work only	138	106	1.36	0.94–2.00
Both at home and at work	383	417	1.05	0.77–1.41
Hours/day-years (home or work)				
<100	278	294	1.00	0.69–1.45
101–200	248	305	0.92	0.63–1.32
>200	333	366	1.02	0.72–1.45

[1]Differences between cell counts and total number of cases and controls included in the analyses are due to missing values.–[2]Adjusted for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family breast cancer history, prior benign biopsy, previous screening mammography, oral contraceptive use and use of hormone replacement therapy.

never exposed to active or passive smoking: the OR (95%CI) were 1.11 (0.85–1.46) for passive smoking only, 1.23 (0.83–1.83) for active smoking only and 1.21 (0.93–1.59) for both active and passive smoking (Table I). Although based on small numbers of women never exposed to active or passive exposure in the reference category, stratified analyses by age showed that the suggestion for an overall increased risk associated with exposure to both active and passive smoking was restricted to younger women (<45 years of age) (2.40 (1.00–5.72), p for heterogeneity by age = 0.07, compared to >50 years). The OR for women exposed only to active smoking in this age-group was 2.97 (0.85–10.34), p value for heterogeneity by age = 0.03, compared to >50 years (data not shown in tables).

Passive smoking

Analyses restricted to never-active smokers showed no significant increase in risk for women ever *versus* never exposed to passive smoking at home or work (1.10 (0.84–1.45); Table I). Women exposed to passive smoking both at home and at work, who might have the highest levels of passive smoking exposure, did not show an elevated risk of breast cancer compared to women never exposed at work or home (1.05 (0.77–1.41); Table I).

There was no evidence of an association between breast cancer risk and increasing levels of passive exposure, as measured by the number of hours per day-years of exposure at home or work (1.02 (0.72–1.45) for women exposed to passive smoking >200 hr/day-years compared to women never exposed to active or passive smoking; Table I). We also observed no significant relationships with the age at first exposure to passive smoking or whether first passive exposure occurred prior to or after a first full-term pregnancy (data not shown). In contrast to expectation, the highest risks were observed among subjects who were exposed to passive smoking later in life (1.30 (0.95–1.78)) or after a first pregnancy (1.33 (0.91–1.93)) (data not shown). Among never-active smokers, passive smoking associations were not significantly modified by age groups (p value for heterogeneity for never *versus* ever exposed to passive smoking = 0.91 and 0.97 for age groups 45–54 and >55 *vs.* <45 years, respectively).

Active smoking

Because of the small number of women without active or passive smoking exposure, and because the risk for women exposed only to passive smoking was similar to that for never-active or passive smokers (1.11 (0.85–1.46)), these two groups of women were combined as a reference category for subsequent analyses.

Overall, most measures of active smoking exposure were not significantly associated with risk, nor was there evidence of significant trends with increasing levels of exposure (Table II). Analyses stratified by age revealed that active smoking habits were related to breast cancer risk among women <45 years of age, but not in women diagnosed at older ages (45–55 and >55). Heterogeneity tests comparing ORs for the young *versus* older age groups were significant for all smoking variables analysed; however, ORs were not significantly different for women 45–55 compared to >55 years of age. Similar associations for active smoking by age were observed when passive smokers were excluded from the reference group, although estimates were more imprecise due to the small number of women in the reference category. ORs (95%CIs) for ever-active *versus* never-active or passive smoking were 4.39 (1.03–18.57), 1.52 (0.7–3.28), and 0.94 (0.51–1.74) for women aged <45, 45–55 and >56, respectively (data not shown in table).

For women <45 years of age, the relative risk for ever compared to never-active smoking was 1.95 (1.38–2.76). Current smokers were at slightly greater risk (2.03 (1.40–2.95)) than former smokers (1.63 (0.97–2.72)). There was a positive trend for smoking duration (p = 0.04) among the younger subjects, with the OR rising to 2.33 (1.32–4.13) for those smoking for 20 or more years (Table II). For women <45 years of age, a statistically sig-

TABLE II – ACTIVE SMOKING CHARACTERISTICS AND BREAST CANCER RISK BY AGE GROUPS IN THE POLISH BREAST CANCER STUDY (2386 CASES AND 2502 CONTROLS)

Age group	Smoking characteristics	Cases[1]	Controls[1]	OR[2]	95% CI	Heterogeneity *p*-value
Smoking status						
All women						
	Never active[3]	1034	1162	1.00	(reference)	
	Ever active	1340	1336	1.10	0.97–1.24	
	Former	504	464	1.09	0.93–1.29	
	Current	836	872	1.12	0.97–1.29	
<45 years						
	Never active[3]	95	135	1.00	(reference)	
	Ever active	208	168	1.95	1.38–2.76	
	Former	51	41	1.63	0.97–2.72	
	Current	157	127	2.03	1.40–2.95	
45–55 years						
	Never active[3]	299	324	1.00	(reference)	
	Ever active	644	655	1.15	0.93–1.40	0.01[4]
	Former	205	195	1.12	0.86–1.47	0.03[4]
	Current	439	460	1.15	0.92–1.43	0.01[4]
>55 years						
	Never active[3]	640	703	1.00	(reference)	
	Ever active	488	511	0.91	0.77–1.09	<0.001[4]
	Former	248	227	1.00	0.80–1.25	0.001[4]
	Current	240	284	0.89	0.71–1.11	<0.001[4]
Average cigarettes per day for ever active smokers[5]						
All women						
	<10	362	358	1.06	0.86–1.31	
	10–14	499	450	1.17	0.97–1.43	
	>14	459	514	0.99	0.83–1.20	
	p for trend[6]				0.42	
<45 years						
	<10	74	56	2.02	1.26–3.27	
	10–14	77	49	2.49	1.53–4.04	Ref.
	>14	57	61	1.35	0.83–2.19	
	p for trend[6]				0.05	
45–55 years						
	<10	174	155	1.26	0.93–1.70	
	10–14	238	225	1.18	0.89–1.55	0.04[7]
	>14	220	270	0.99	0.76–1.30	
	p for trend[6]				0.08	
>55 years						
	<10	114	147	0.73	0.54–0.98	
	10–14	182	176	1.00	0.77–1.30	<0.001[7]
	>14	182	182	0.97	0.75–1.25	
	p for trend[6]				0.11	
Total duration of smoking in years for ever active smokers[5]						
All women						
	<10	457	437	1.04	0.85–1.29	
	10–20	329	325	1.06	0.85–1.32	
	>20	530	555	0.99	0.83–1.20	
	p for trend[6]				0.86	
<45 years						
	<10	91	76	1.57	1.01–2.44	
	10–20	73	61	1.83	1.15–2.91	Ref.
	>20	41	29	2.33	1.32–4.13	
	p for trend[6]				0.04	
45–55 years						
	<10	206	215	1.01	0.76–1.34	
	10–20	154	161	1.07	0.79–1.45	0.04[7]
	>20	274	273	1.07	0.82–1.39	
	p for trend[6]				0.78	
>55 years						
	<10	160	146	0.95	0.71–1.27	
	10–20	102	103	0.86	0.62–1.20	0.001[7]
	>20	215	253	0.78	0.61–0.99	
	p for trend[6]				0.08	
Age started smoking in years for ever active smokers[5]						
All women						
	<17	110	127	1.07	0.80–1.42	
	17–19	479	428	1.23	1.04–1.46	
	20–24	473	489	1.03	0.87–1.21	
	>24	258	278	1.10	0.90–1.34	
	p for trend[6]				0.93	

TABLE II – ACTIVE SMOKING CHARACTERISTICS AND BREAST CANCER RISK BY AGE GROUPS IN THE POLISH BREAST CANCER STUDY (2386 CASES AND 2502 CONTROLS) (CONTINUED)

Age group	Smoking characteristics	Cases[1]	Controls[1]	OR[2]	95% CI	Heterogeneity *p*-value
<45 years						
	<17	31	28	1.96	1.08–3.56	
	17–19	84	65	2.19	1.42–3.39	Ref.
	20–24	76	61	1.77	1.13–2.78	
	>24	15	12	1.86	0.79–4.26	
	p for trend[6]				0.6	
45–55 years						
	<17	56	70	1.01	0.67–1.51	
	17–19	254	239	1.21	0.94–1.56	0.08[7]
	20–24	248	241	1.18	0.92–1.52	
	>24	76	101	0.96	0.67–1.36	
	p for trend				0.61	
>55 years						
	<17	23	29	0.84	0.47–1.52	
	17–19	141	124	1.03	0.77–1.36	0.02[7]
	20–24	149	187	0.70	0.54–0.91	
	>24	167	165	1.10	0.86–1.41	
	p for trend[6]				0.81	
Smoking initiation in relation to 1st full-term pregnancy (among parous ever active smokers)[5]						
All women						
	After	273	335	1.06	0.87–1.29	
	Before	839	819	1.14	0.98–1.32	
<45 years						
	After	33	22	2.40	1.27–4.53	Ref.
	Before	154	123	2.03	1.40–2.94	
45–55 years						
	After	91	130	1.02	0.73–1.43	0.01[7]
	Before	446	453	1.15	0.92–1.43	
>55 years						
	After	152	183	0.96	0.74–1.24	<0.001[7]
	Before	239	243	0.90	0.72–1.13	

[1]Differences between cell counts and total number of cases and controls are due to missing values.–[2]Adjusted for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family breast cancer history, prior benign biopsy, previous screening mammography, oral contraceptive use and use of hormone replacement therapy (HRT). Smoking duration and intensity are adjusted for each other (see Material and Methods).–[3]Never smokers within age category comprise the reference category.–[4]*p* for heterogeneity by age, compared to <45 years.–[5]Never smokers for all women or within each age group are the reference category.–[6]Test for trends among exposed only.–[7]*p* for heterogeneity by age, compared to <45 years. Test for dose, intensity, and age started smoking assume a log-linear relationship between increasing levels of exposure and breast cancer risk, within each age category. Tests for smoking initiation in relation to first pregnancy are 2-degrees for freedom LRT comparing a model with interaction terms for age and indicator terms for smoking initiation before or after pregnancy, to a model without the interactions terms.

nificant increasing trend ($p = 0.003$) in risk was seen with pack-years of smoking, with an OR of 2.44 (1.47–4.05) for the highest exposure category (>10 pack-years). In contrast, no association with pack-years was observed among the other age-groups (p for trend = 0.65 and 0.51 for women 45–55 and >55 years of age respectively; data not shown in table).

There were no clear linear trends with number of cigarettes smoked per day or with age at which smoking commenced. Among the younger study subjects, there were also no significant differences in risk according to whether smoking was initiated prior to or after a first full-term pregnancy, or whether smoking commenced before or after menarche (data not shown).

Among the total series of subjects, smoking associations were similar when data were stratified by other hormonally mediated risk factors such as parity and BMI (data not shown). Among the women <45 years of age, the risk associated with ever-active smoking tended to be higher for obese women (5.48 (1.72–17.52) for BMI > 30) than for thinner women (1.41 (0.87–2.29) and 2.52 (1.21–5.27) for BMI < 25 and BMI > 25–30, respectively; p for heterogeneity = 0.05; data not shown in Table).

Modification of smoking associations with breast cancer risk by tumor ER and PR status

ER status was determined in 1723 (72%) cases, with 1132 (66%) positive (ER+) and 591 (34%) negative (ER−). PR status was available for 1715 (72%) cases, with 946 (55%) positive (PR+) and 769 (45%) negative (PR−).

Table III shows the overall association between cigarette smoking characteristics and breast cancer by ER tumor status. Associations for smoking status, intensity and duration were similar for ER+ and ER− tumors, although somewhat stronger relations related to early smoking initiation were seen for ER+ tumors (Table III). Differences between ER+ and ER− tumors remained nonsignificant after women exposed to passive smoking were excluded from the reference category (OR = 1.33, 95% CI: 0.94–1.88 for ER+ and OR = 1.17, 95% CI: 0.75–1.83 for ER-tumors for ever *vs.* never smoking women; p for heterogeneity = 0.49; data not shown). Analyses stratified by age did not show consistent differences in risk by ER status in any age group (age-specific estimators not shown). PR status did not modify associations between active smoking characteristics and breast cancer risk (data not shown). Similarly, the ORs for passive smoking and breast cancer risk were not modified by ER or PR status (data not shown).

Stratified analyses by other tumor characteristics such as size (≤2 cm *vs.* >2 cm), nodal status (negative *vs.* positive) and histology (ductal, lobular, mixed, tubular, other) indicated that the smoking associations were not significantly modified by these tumor characteristics, although among younger women risk was somewhat higher for smokers with smaller tumors (≤2 cm) and negative nodes (2.23 (1.42–3.52)) than for those with larger

TABLE III – SMOKING ASSOCIATIONS WITH BREAST CANCER RISK BY TUMOR ESTROGEN RECEPTOR STATUS IN THE POLISH BREAST CANCER STUDY (2386 CASES AND 2502 CONTROLS)

Smoking Status	ER+			ER−			Heterogeneity (*p*-value)
	Cases[1] (*N* = 1128)	OR[2]	95% CI	Cases[1] (*N* = 588)	OR[2]	95% CI	
Never active	481	1.00	(reference)	262	1.00	(reference)	
Ever active	647	1.16	0.99–1.36	326	1.04	0.86–1.27	0.27
Average number of cigarettes per day							
<10	174	1.06	0.82–1.37	90	1.07	0.77–1.48	0.36
10–14	247	1.26	0.99–1.60	117	1.13	0.84–1.53	
>14	221	1.02	0.81–1.29	117	0.73	0.73–1.32	
Total duration of smoking in years							
<10	221	1.09	0.84–1.41	103	0.94	0.68–1.31	0.59
10–20	165	1.15	0.87–1.51	85	1.02	0.73–1.44	
>20	255	1.02	0.81–1.29	135	0.98	0.73–1.32	
Age started smoking							
<17	56	1.24	0.87–1.77	29	1.04	0.67–1.63	0.56
17–19	246	1.41	1.15–1.75	119	1.18	0.90–1.53	
20–24	220	1.01	0.82–1.24	114	0.98	0.75–1.27	
>24	120	1.09	0.85–1.40	62	1.02	0.75–1.40	
Smoking initiation in relation to 1st full term pregnancy for parous women							
After	117	0.99	0.77–1.29	79	1.13	0.84–1.53	0.37
Before	416	1.25	1.04–1.50	193	1.03	0.82–1.30	

[1]Differences between cell counts and total number of cases are due to missing values.–[2]Adjusted for age, site, education, age at menarche, number of full-time births, age at first full-term birth, age at menopause, BMI, family breast cancer history, prior benign biopsy, previous screening mammography, oral contraceptive use, and use of hormone replacement therapy (HRT). Smoking duration and intensity are adjusted for each other, by combining nonsmokers with the lowest exposure category (duration or intensity respectively). (See Material and methods).

TABLE IV – *NAT2* GENOTYPE, SMOKING STATUS AND BREAST CANCER RISK IN THE POLISH BREAST CANCER STUDY (1995 CASES AND 2296 CONTROLS WITH DNA)

	NAT2 rapid/intermediate acetylators				*NAT2* slow acetylators				Heterogeneity *p*-value
	Cases[1]	Controls[1]	OR[2]	95% CI	Cases[1]	Controls[1]	OR[2]	95% CI	
NAT2 association with breast cancer risk									
	778	895	1.00	(reference)	1122	1305	0.99	0.87–1.13	
Smoking status and *NAT2* association with breast cancer risk									
All women									
Never	333	395	1.00	(reference)	465	620	0.89	0.73–1.09	
Ever	443	496	1.04	0.85–1.29	652	684	1.12	0.92–1.36	0.17
Women <45 years of age									
Never	30	69	1.00	(reference)	44	75	0.87	0.45–1.68	0.37
Ever	46	73	1.65	0.87–3.16	104	77	2.10	1.13–3.89	

[1]Analyses were limited to cases and controls that provided DNA. Differences between cell counts and total number of cases and controls are due to missing values.–[2]Adjusted for age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family breast cancer history, prior benign biopsy, previous screening mammography, oral contraceptive use and use of hormone replacement therapy (HRT).

tumors (>2 cm) and positive nodes (1.63 (1.02–2.61)); however, heterogeneity tests by tumor size and nodal status were not statistically significant (data not shown).

NAT2 *acetylation genotype and cigarette smoking*

NAT2 slow acetylation was not associated with a significantly increased risk of breast cancer compared to rapid/intermediate acetylators, overall (Table IV) or by categories of age at diagnosis. The association between ever *versus* never smoking was some what stronger for *NAT2* slow than rapid/intermediate acetylators, particularly for women <45 years of age; however, tests for interaction were not statistically significant (Table IV). Trends for increasing smoking duration or intensity were not more apparent in slow than rapid accelerators (data not shown). Evidence for a smoking association among *NAT2* slow acetylators was somewhat strengthened after excluding passive smokers from the reference category: OR (95%CI) among *NAT2* slow acerylators for ever *versus* never-active smoking was 1.26 (1.05–1.51), and it became 1.57 (1.06–2.34) when we compared ever-active to never-active or passive smokers (data not shown).

Discussion

In a large population-based study in Poland, we found no overall association of smoking and breast cancer risk, although data suggested that active smoking may increase risk for breast cancer among women younger than 45 years of age. The association was particularly apparent for smokers of longer durations. In contrast, analyses of lifetime exposures to passive smoke at home and work showed no association with breast cancer risk, despite our having detailed information on these exposures.

Most previous studies on passive smoking and breast cancer did not assess exposures from all potential sources (childhood exposure from parents and adult exposure at home and at work). Although most studies, including large cohort studies,[6,39] have reported no substantial associations between passive smoking and breast cancer risk,[6,32,40–42] it has been suggested that risk estimates could be underestimated due to failure to consider all sources of passive exposure.[4] This explanation is not supported by our study, given that we had detailed information on the main lifetime sources of passive smoking and still did not observe any associations for exposures at work, at home or in both locales.

Some recent studies suggest that the inclusion of passive smokers in the referent group may have biased previous findings for active smoking towards the null.[2,4,6,10] Although we included subjects with passive smoking in our reference group for most analyses because we had few women totally unexposed to either active and passive smoking, our risks for active smoking were not altered when we used a ''pure'' reference group comprised of individuals never exposed to any type of smoking.

One of the largest assessments of the effect of active smoking on breast cancer risk derives from a recent pooled analysis of 53 epidemiological studies (58,515 cases and 95,067 controls).[3] The only exposure variable examined in this collaborative effort was whether women had ever smoked, with no further information available on amount smoked, age that smoking started, duration of smoking or passive smoking. Their OR estimates for ever *vs.* never smoking, based on all 53 studies, was 1.03 (SE = 0.02); and when analyses were limited to 33 population-based case-control studies the OR was 1.07 (SE = 0.03). These estimates are consistent with our overall estimate for ever smokers (1.10 (0.97–1.24)). Based on limited analyses of smoking habits in this large pooled analysis, the authors concluded that cigarette smoking has no effect on the overall risk of breast cancer, but they indicated that an association among certain groups of women could not be ruled out.

Indeed, our findings indicated that age at diagnosis might modify the association between active smoking and breast cancer risk. Among women diagnosed at young ages (<45 years of age), risk was higher for current as opposed to former smokers and greater for women who had smoked for 20 or more years. This suggested that the lack of or only minimal relationship between tobacco smoking and breast cancer risk observed in most previous case-control studies could be explained by failure to account for effect modification by age. Recent large cohort studies in very young (20–45 years of age)[8,42] and middle-aged women (40–59 years of age)[7] have suggested increases in risk for women with long durations of exposure to smoking and early ages at initiation. Our results are consistent with findings from these large cohort studies conducted in very young women but not with the one conducted in middle-aged women. Most previous studies, however, that have examined smoking in relation to breast cancer risk among both premenopausal and postmenopausal women have not shown significant differences in risk according to menopausal status.[2,6] If the relevant modifying factor is age rather than menopausal status, previous studies of premenopausal women might have underestimated estimates by diluting associations present only in younger women (<45 years). Although our series of young women is not large, our sample size was large enough to contrast this group of women with older women. An association between cigarette smoking and breast cancer limited to young women is biologically plausible since chemicals in tobacco smoke could be breast carcinogens,[14,43] and their effects are believed to be dependent on the stage of mammary tissue differentiation, *i.e.* the less differentiated the mammary tissue, the more effective these compounds are in inducing cancer.[9,44] Finally, we did not find a stronger association among women who began smoking before their first full-term pregnancy or menarche, as previously suggested by some studies.[9,45]

Our data suggested that smoking has similar relationships for ER+ and ER− tumors, as also found in a recent review by Althuis *et al.*,[21] which included mainly case-control studies of modest sizes. Although a recent large cohort study among premenopausal women aged 25–42 years suggested a relationship between active smoking and ER+ breast cancers, the interaction between ER status and smoking was not significant.[8] Our data are weakly consistent with an association between early age at initiation and ER+ tumors; however the association was primarily seen for women who initiated smoking between ages 17–19 years of age, with lower risks observed among those with earlier ages at initiation (possibly reflecting small numbers in this subgroup). Another, relatively small, prospective cohort study conducted among postmenopausal women found an increased risk of breast cancer associated with active smoking only in women with high blood levels of estrogens,[46] providing some support for a hormone-mediated relationship.[14]

Smoking could also affect breast cancer risk through a direct toxic effect resulting in DNA damage.[27,28,47] Slow *NAT2* acetylation genotypes may be associated with a diminished ability to detoxify carcinogenic arylamines in tobacco smoke, thereby increasing cancer risk.[48] However previous studies have not demonstrated an association between *NAT2* genotype and breast cancer risk,[33,49–51] and only a few have suggested increased risk among smokers who are slow acetylators.[31,52,53] Our data do not support this hypothesis. Given that breast epithelium produces only low levels of *NAT2*, it is likely that this enzyme plays a minor role in detoxification pathways in the breast.[54]

Strengths of our study included a population-based study design, large sample size that facilitated age-stratified analyses, and detailed tumor characterization including ER and PR status. Although this study has among the highest participation rates attained in population-based case-control studies with collection of biological specimens,[55] selection bias cannot be ruled out. Recall bias for smoking could explain small associations; however, previous evaluation of the impact of recall bias in studies of tobacco smoking and lung cancer have indicated that such biases are likely to be small.[56] In addition, it is unlikely that recall bias is stronger for younger than for older women. Our findings also may have been limited by possible misclassification of ER/PR status, given that assays were performed in three different locations (one laboratory in Warsaw and two in Łódź), which could have diluted our findings. Further, the relatively small number of young women in this study resulted in low power to detect associations in analyses stratified by hormone receptor status.

In conclusion, results from this large population-based case-control study support a moderate excess risk associated with active smoking for early onset breast cancers. Passive smoking is unlikely to be related to a substantial increase in breast cancer risk. In light of recent increases in smoking among young women worldwide, additional studies of these relationships are warranted. In Poland, where smoking prevalence is high and rising among young women, even if the risk associated with this exposure and breast cancer is small, its effect could still account for a substantial number of breast cancer cases.

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